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Formulation and Characterization of Macitantan Nanoparticles for the Treatment of Pulmonary Hypertension

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Abstract: ***Nanomedicine is an emerging field with great opportunities to improve the treatment of diseases which are currently not curable. Pulmonary arterial hypertension (PAH) is one of these diseases treatable by inhalation of medicines that provide novel depots for drugs with short pharmacological half - lives to improve the quality of life for patients. In this study, positively charged nanoparticles based on chitosan were developed and synthesized to enhance penetration capability of Macitentan in order to improve the treatment to cure pulmonary arterial hypertension (PAH). This study focuses on the design and characterization of drug delivery systems with the potential to improve the treatment options for hypertonic conditions (like PAH).***

Keywords: Pulmonary arterial hypertension, Nanoparticles, preparation, characterization

1. Introduction

Pulmonary arterial hypertension (PAH) is one form of a broader condition known as pulmonary hypertension, which is high blood pressure in the lungs. In PAH, this increased pressure in the vessels is caused by obstruction in the small arteries in the lung for a variety of reasons.[1, 2, 3] There are four stages of pulmonary arterial hypertension. Class 1; the condition doesn't limit your physical activity. Class 2; the condition slightly limits your physical activity. Class 3; the condition significantly limits your physical activity. Class 4; condition where you are unable to carry out any type of physical activity without symptoms.[4, 5.6]

Symptoms of PAH include shortness of breath (dyspnea) especially during exercise, chest pain, and fainting episodes. The exact cause of PAH is unknown and although treatable, there is no known cure for the disease.[7] PAH usually affects women between the ages of 30 - 60. Individuals with PAH may go years without a diagnosis, either because their symptoms are mild, nonspecific, or only present during demanding exercise.[8] However, it is important to treat PAH because without treatment, high blood pressure in the lungs causes the right heart to work much harder, and over time, this heart muscle may weaken or fail.[9] The progressive nature of this disease means that an individual may experience only mild symptoms at first, but will eventually require treatment and medical care to maintain a reasonable quality of life.[10]

Macitentan is an orphan drug for the treatment of pulmonary arterial hypertension (PAH). Endothelin - 1 (ET - 1) plays a critical role of pathophysiology of PAH. Macitentan, a new dual endothelin receptor antagonist, has reportedly improved prognosis of PAH patients by delaying the progression of disease. It prevents the binding of ET - 1 to both endothelin A (ETA) and endothelin B (ETB) receptors.[11]

Macitentan is an endothelin receptor antagonist (ERA). Macitentan, sold under the brand name Opsumit. This drug is developed by Actelion and approved for the treatment of pulmonary arterial hypertension (PAH).[1] [2] The other two ERAs marketed as of 2014 are bosentan and ambrisentan. [13] Macitentan is a dual ERA, meaning that it acts as an antagonist of two endothelin (ET) receptor subtypes, ET_A and ET_B. [13] However, macitentan has a 50 - fold increased selectivity for the ETA subtype compared to the ETB subtype. [14] The drug received approval from the U. S. Food and Drug Administration (FDA) on October 13, 2013. Macitentan is available as a generic medication in the United States as of April 2021. [15]

Endothelin (ET) is an extremely potent blood vessel constricting substance that is secreted by endothelial cells. In the lungs, the most common ET form released is ET - 1. ET - 1 release can occur through both constitutive and non - constitutive pathways. Upon release, ET - 1 can bind to the ET receptors that are expressed on arterial smooth muscle cells and fibroblasts in the lungs. ET receptors are G protein coupled receptors and, when activated, lead to an increase in intracellular calcium levels via the Gαq signaling pathway. There are two receptor subtypes that endothelin will bind to: ETA and ETB. ETA is associated with cell growth and vasoconstriction while ETB is responsible for anti - proliferation of cells, vasodilation and ET - 1 clearance. The rise in intracellular calcium leads to contraction of the arterial smooth muscle, as well as vascular remodelling due to cell proliferation. Prolonged constriction and fibrosis are factors in the pathogenesis of PAH.[16]

Macitentan blocks the ET1 - dependent rise in intracellular calcium by inhibiting the binding of ET - 1 to ET receptors. Blocking of the ETA receptor subtype seems to be of more importance in the treatment of PAH than blocking of ETB, likely because there are higher numbers of ETA receptors than ETB receptors in pulmonary arterial smooth muscle cells. The blocking of Endothelin 1 leads to vasodilation and decreases the proliferation of cells in the vessels of the artries which contributes to the narrowing and leads to the pulmonary arterial hypertension.

The mucosa of the nasal cavity is thin and well vascularized, and so the administered drug can be transferred into the systemic circulation quickly. Other advantages of drug delivery via this route are the avoidance of the hepatic first - pass metabolism and the possibility of systemic and local effect. Limitations for this route include the limited volume of the administered formulation, which restricts the application for potent drugs, and also it is not suitable for long - term or frequently administered drugs because of the harmful effect on the nasal epithelium.[17] Drugs of low and high molecular weight have been successfully delivered using this route, steroids, antiasthmatic, anesthetics, antihistaminic, antiemetic, sedatives, antimigraine, peptides, peptide analogs such as desmopressin, hormones, vaccines, and most recently drug delivery to the brain for primary meningoencephalitis.[18, 19]

The process of drug delivery via the nasal route is challenging due to the short residence time of the drug, high nasal secretion rate, and low permeability of the nasal membrane. Drug physicochemical properties such as surface charges, hydrophilicity/ hydrophobicity, partition coefficient, degree of ionization, and molecular size are very important factors that could affect the drug transport by this route.[20] Different nasal drug delivery systems have been studied and illustrated a potential application in this field. Among those, chitosan particles demonstrated some achievement in the nasal delivery of proteins, vaccines, and other therapeutic agents. The mucoadhesive properties accompanied with the small particle size facilitate both retention and permeation of the administered drug - loaded particles. Insulin - loaded chitosan micro - and nanoparticles showed a considerable decrease in blood glucose level after their nasal administration into rats and rabbits, respectively.[21, 22] Chitosan nanoparticles adsorbed with ovalbumin and cholera toxins induced systemic immune response in rats and were effective for targeting to nasal - associated lymphoid tissues in nasal vaccine delivery. Induction of IgA antibodies at different mucosal sites in the body such as upper and lower respiratory tract, and small and large intestine as a result of the distribution of the intranasal administered antigen - loaded chitosan particles have been reported.[23] Mice that were intranasally immunized with chitosan microspheres loaded with Bordetella bronchiseptica antigens showed significantly higher B. bronchiseptica–specific IgA antibody responses in saliva and serum, with high mice survival rate.[24]

2. Materials and Methods

Macitentan was received as a gift sample from Cadila Healthcare, (Ahmedabad, India). Chitosan was purchased from Sigma Aldrich (New Delhi, India). Sodium tripolyphosphate (TPP) was purchased from Central Drug House (Delhi, India) and Tween - 80 was supplied by S. D. Fine Chemicals (New Delhi, India). All other chemicals were of analytical grade and used as received.

Preparation of chitosan nanoparticles

Chitosan nanoparticles were prepared by ionic cross linking of chitosan solution (with or without drug) with TPP prepared in the presence of Tween 80 as a resuspending agent to prevent particle aggregation, at ambient temperature while stirring. Cholinesterase inhibitor - loaded chitosan nanoparticles were prepared as described above by dissolving 10 mg of cholinesterase inhibitor in 10 ml chitosan solution (0.1, 0.2, 0.3, 0.4 and 0.5% w/v) containing 0.5% w/v Tween 80 before adding TPP (0.25% w/v). The nanoparticle suspensions were centrifuged at 12 000×g for 30 min using C24 centrifuge (Remi Centrifuge, Mumbai, India). The supernatant was analyzed by UV spectrophotometry to calculate the % drug entrapment and drug loading.

3. Results and Discussion

The Macitentan chitosan nanoparticles were prepared and characterized for the particle size, morphology and particle size distribution. The chitosan nanoparticles had a particle diameter ranging from 100 - 200 nm and the shape was spherical when analyzed by quasi electron laser spectrophotometer (QELS) and scanning electron microscopy (SEM), respectively. The nanoparticles showed a loading efficiency up to 92% and a loading capacity up to 50% (w/w). These studies showed that the submicron size range achieved for the chitosan nanoparticles, the mucoadhesive property of chitosan and ability of Tween 80 will provide effective delivery of Macitentan from nasal route. In vitro permeation study showed that the nanoparticles promoted an increase in the flux of the drug through the nasal mucosa. In view of these results, chitosan nanoparticles were found to be a promising approach and these results suggest that the chitosan containing nanoparticles have great potential for nasal Macitentan administration. Thus, chitosan nanoparticles possess a potential to deliver drug through the nasal mucosa for the treatment of pulmonary arterial hypertension.

4. Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest

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